sub B + cont'd

(ii) a sequence complementary to all or part of the second open reading frame of (i); and

(iii) a sequence encoding an untranslated RNA molecule, or complement thereof;

wherein said second nucleotide sequence is operably linked to a promoter which is activated by said non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase.--

Remarks

Reconsideration of this Application is respectfully requested.

After cancellation of claims 1-74 and entry of the foregoing amendments, claims 75-125 will be pending in the application, with claims 75, 102, 103 and 125 being the independent claims.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider and withdraw all outstanding objections and rejections.

I. The Claimed Invention

The claims pending in the captioned application are directed to nucleic acid molecules which encode RNA molecules comprising (a) at least one *cis*-acting sequence element, (b) a first open reading frame having a nucleotide sequence encoding a non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase, and (c) at least one second nucleotide sequence which is selected from the group consisting of (i) a second open reading frame encoding a protein, or portion thereof, wherein the second open reading frame is in a translatable format after one or more RNA-dependent RNA replication events; (ii) a sequence complementary to all or part of the second open reading frame of (i); and (iii) a sequence encoding an untranslated RNA molecule, or complement thereof,

wherein the second nucleotide sequence is operably linked to a promoter which is activated by the non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase.

The pending claims are further directed to methods for preparing and using the above described nucleic acids, as well as expression products of these nucleic acids.

II. New Claims 75-125

In order to simplify the amendments to the claims, Applicants have canceled claims 1-74 and submit herewith new claims 75-125. For the Examiner's convenience, Table 1 below provides a cross-reference between the canceled independent claims and the new independent claims submitted herewith.

Table 1.

Canceled Independent Claim	Corresponding New Independent Claim
1	75
15	102
38	103
74	125

Each of new claims 75 and 79-125 are supported, *inter alia*, by claims originally filed with the captioned application. New claims 76-78 are supported, *inter alia*, by Figure 1 of the application.

III. The Amendments to the Specification

The specification has also been amended to correct a number of typographical errors. None of these amendments introduce new matter and their entry is respectfully requested.

IV. Claims 5 and 7

The Examiner has withdrawn the subject matter of claims 5 and 7 from consideration and has indicated that the subject matter of claims 1-4, 6, 8-34, 38-70, and 74 is under consideration in the captioned application. (Paper No. 11, pages 1 and 2.)

The Examiner supports the removal of the subject matter of claims 5 and 7 from consideration by referring to 37 C.F.R. § 1.142(b) and stating that these claims "are drawn to a nonelected species . . . ." (Paper No. 11, page 2.) Applicants respectfully note that 37 C.F.R. § 1.142 is directed to restriction requirements, not elections of species.

Applicants assert that the withdrawal of the subject matter of claim 5 from consideration is improper and point out that canceled claim 5 reads on the elected species (*i.e.*, erythropoietin). Thus, the Examiner should consider the patentability of the subject matter of claim 5 at the present time.

Further, the subject matter of canceled claims 5 and 7, submitted herein as new claims 83 and 85, is fully embraced within canceled claim 1, submitted herein as new claim 75. Thus, regardless of whether the Examiner considers the patentability of the subject matter of claim 5 at the present time, it is Applicants' understanding that the Examiner will consider the patentability of the subject matter of claims 83 and 85 if claim 75 is found to be in condition for allowance. (*See* MANUAL OF PATENT EXAMINING PROCEDURE, Seventh Edition, Revision 1, (February 2000) (M.P.E.P.) § 809.02(c)(B).)

In view of the above, Applicants respectfully request that the Examiner consider the patentability of claims 83 and 85 at the present time.

V. The Rejections of the Claims under 35 U.S.C. § 112, First Paragraph

A. Written Description

The Examiner has rejected claims 1-4, 6, 8-14, 16-34, 38-70, and 74 of the captioned application under 35 U.S.C. § 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." (Paper No. 11, page 3.)

The Examiner directs Applicants to the U.S. Patent and Trademark Office's Revised Interim Written Description Guidelines (Written Description Guidelines) and then states that:

> In this case, *Applicant describes only a single species, comprised by SEQ ID NO: 1, by complete structure*.... The specification describes the characteristics required to qualify as a member of the claimed genus, as well as methods which one might employ in order to isolate a member of the genus, however it describes no single species which comprises all of the characteristics required, *other than SEQ ID NO: 1*. This disclosure is not deemed sufficient to reasonably convey to one skilled in the art that applicant was in possession of the [sic] more than a single species of the claimed genus at the time of filing, and the written description requirement is not satisfied.

(Paper No. 11, pages 3-4 (emphases added).) Applicants understand the Examiner's position to be that the disclosure of a single species is insufficient to support generic claims, even when the characteristics of genus members are described. Applicants respectfully disagree.

Applicants begin by noting that the Examiner's position is in open conflict with the Federal Circuit's position in *Univ. of Calif. v. Eli Lilly & Co.*, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997), as well as the U.S. Patent and Trademark Office's own Written Description Guidelines. (*See, e.g.,* Written Description Guidelines, page 31 ("The disclosure of a single species may provide an adequate written description of a genus when the species is representative of the genus.").)

In order to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, the specification must convey with reasonable clarity to one skilled in the art that the applicant was in

possession of the claimed invention as of the filing date sought. *Vas-Cath Inc. v. Mahurkar*, 19 U.S.P.Q.2d 1111, 1117 (Fed. Cir. 1991). Further, an adequate written description may be provided by drawings. *Vas-Cath Inc.*, 19 U.S.P.Q.2d at 1118-1120.

According to the Written Description Guidelines:

> There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed. If the examiner determines that the application does not comply with the written description requirement, *the examiner has the initial burden, after a thorough reading and evaluation of the content of the application, of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims. . . .*

(Written Description Guidelines, page 4 (emphasis added).)

The Examiner has, in essence, merely stated that the disclosure of one species is insufficient to provide an adequate description of a genus. Further, the Examiner has provided no "evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims." (Written Description Guidelines, page 4.) The Examiner must provide such evidence or reasons to make and maintain a rejection of the claims under 35 U.S.C. § 112, first paragraph, for lack of written description. Thus, the Examiner's initial burden of proof for rejecting canceled claims 1-4, 6, 8-14, 16-34, 38-70, and 74 as not being supported by an adequate written description clearly has not been met and the rejection should be withdrawn.

While not wishing to prejudice Applicants' position that the Examiner has provided insufficient evidence or reasons to make and maintain a rejection of the claims for lack of written description, Applicants assert that one skilled in the art reviewing the captioned application would clearly recognize that Applicants were in possession of the invention defined by canceled claims 1-4, 6, 8-14, 16-34, 38-70, and 74 and new claims 75-125.

The Federal Circuit recently stated in *Univ. of Calif. v. Eli Lilly & Co.*, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997), that:

> In claims to genetic material . . . a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. *It does not define any structural features commonly possessed by members of the genus that distinguish them from others.* One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. . . .
>
> Thus, as we have previously held, a cDNA is not defined or described by the mere name "cDNA," even if accompanied by the name of the protein that it encodes, but requires a kind of specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the cDNA. *See Fiers*, 984 F.2d at 1171, 25 USPQ2d at 1606. *A description of a genus of cDNAs may be achieved by means of a recitation of* [1] *a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or* [2] *of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.* . . . We will not speculate in what other ways a broad genus of genetic material may be properly described, . . .

Univ. of Calif., 43 U.S.P.Q.2d at 1406 (emphases added) (citations omitted) (footnote omitted). Thus, the Federal Circuit has indicated that the written description requirement for generic claims directed to genetic material, such as cDNA, may be satisfied by providing the sequences of a representative number of nucleic acids which fall within the scope of the genus *or* by providing a recitation of structural features which are common to a substantial portion of the members of the genus. *See Univ. of Calif.*, 43 U.S.P.Q.2d at 1406.

The claims in the captioned application are not directed, as was the case in *Univ. of Calif. v. Eli Lilly & Co.*, to genera like "vertebrate" or "mammalian" based only on one example of a mammal (*i.e.*, a rat). *See Univ. of Calif.*, 43 U.S.P.Q.2d at 1401. The claims in the captioned application are thus not based on vague taxonomic names such as "vertebrate," "mammal," "rat," or "human" but

are based instead on structural elements which are clearly set forth in the specification and were clearly in the possession of the inventors in March of 1998.

Applicants note that the new claims submitted herewith, which are exemplified by claim 75, contain recitations of structural features which are common to *all* of the members of the genera that fall within their literal scope. More specifically, in order for nucleic acids and methods to fall within the literal scope of the new claims submitted herein, these nucleic acids and methods must have the specific recited features.

Using claim 75 as an example, DNA molecules of the invention which fall within the literal scope of this claim encode RNA molecules which comprise (1) at least one *cis*-acting sequence element, (2) a first open reading frame having a nucleotide sequence encoding a non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase, and (3) at least one second nucleotide sequence comprising an open reading frame which encodes a polypeptide, a sequence complementary to all or part of an open reading frame, or an untranslated RNA (*e.g.*, an antisense RNA, a tRNA, a rRNA, or a ribozyme), wherein the second nucleotide sequence is operably linked to a promoter which is activated by the non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase. Thus, Applicants have provided specific structural characteristics of nucleic acids which fall within the literal scope of claim 75.

As recognized by the Examiner, Applicants have further provided a specific species, defined by SEQ ID NO:1, which exemplifies nucleic acids of the invention. Applicants note that Figure 1 of the captioned application provides a graphical representation of one embodiment of the invention.

Assuming, *arguendo*, that satisfaction of the written description requirement requires the disclosure of more than one species which fall within the scope of the claims, Applicants assert that a considerable number of such species are disclosed in the captioned application and have actually been produced by Applicants. For example, at page 43, lines 6-8, the specification states that five specific species which fall within the literal scope of claim 75 have been constructed. These species are modified forms of the pCYTts vector which contain nucleic acids encoding green fluorescent

protein (GFP), secreted alkaline phosphatase (SEAP), β-interferon (β-INF), erythropoietin (EPO), and HIV gp160 in the position of the second open reading frame.

The captioned application also states that nucleic acids encoding a considerable number of other proteins and RNAs can be inserted in the position of the second nucleotide sequence. (*See, e.g.*, Specification, page 25, line 24, to page 27, line 11.) When the degeneracy of the genetic code is considered, in instances where the second open reading frame encodes a protein, the number of disclosed species which fall within the literal scope of the claims becomes immense.

The specification further states that, in addition to the second nucleotide sequence, various genetic elements (*e.g.*, RNA-dependent RNA polymerase coding sequences and subgenomic promoters) may be used to construct nucleic acids of the invention. (*See, e.g.*, Specification, page 21, line 19, to page 22, line 25.) As discussed below with respect to enablement issues, a considerable number of these genetic elements are disclosed in publications which are referred to in the specification.[2]

While not wishing to appear as endorsing the U.S. Patent and Trademark Office's Written Description Guidelines, Applicants note that the invention defined by new claim 75, for example, is similar to a claim presented in Example 14 of these Guidelines. More specifically, Example 14 of the Written Description Guidelines discusses a claim which reads as follows: "A protein having SEQ ID NO: 3 and variants thereof that are at least 95% identical to SEQ ID NO: 3 and catalyze the reaction of A → B." (Written Description Guidelines, pages 53-55.)

Example 14 of the Written Description Guidelines then states:

> The specification exemplifies a protein isolated from liver that catalyzes the reaction of A → B. The isolated protein was sequenced and was determined to have the sequence as set forth in SEQ ID

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[2]Applicants note that the publications disclosed in the captioned application have been incorporated by reference. (Specification, page 57, lines 8-10.) Applicants do not believe that it is necessary to amend the specification or sequence listing to introduce material from these publications to provide an adequate written description for new claims 75-125, but Applicants will do so at the request of the Examiner.

> NO: 3. The specification also contemplates but does not exemplify variants of the protein wherein the variant can have any or all of the following: substitutions, deletions, insertions and additions. The specification indicates that procedures for making proteins with substitutions, deletions, insertions and additions is routine in the art and provides an assay for detecting the catalytic activity of the protein.

(Written Description Guidelines, page 53.) The following discussion of the exemplary claims is then provided:

> The claim has two different generic embodiments, the first being a protein which comprises SEQ ID NO: 3 and the second being variants of SEQ ID NO: 3. *There is a single species disclosed, that species being SEQ ID NO: 3.*
>
> * * *
>
> There is actual reduction to practice of the single disclosed species. The specification indicates that the genus of proteins that must be variants of SEQ ID NO: 3 does not have substantial variation since *all of the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO: 3.* The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO: 3 which are capable of the specified catalytic activity. *One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.*

(Written Description Guidelines, pages 54-55 (emphases added).) Example 14 further states that the claim discussed therein is supported by an adequate written description. (Written Description Guidelines, page 55.)

Applicants assert that new claim 75, as well as the other claims pending in the captioned application, like the claim set out in Example 14 of the U.S. Patent and Trademark Office's Written Description Guidelines, is supported by an adequate written description. This is so because one skilled in the art reviewing the captioned application would recognize that Applicants were in possession of the genera of nucleic acids which fall within the scope of these claims, as well as methods for making and using these nucleic acids.

In view of the above, Applicants assert that the written description requirement has been satisfied for the new claims submitted herein. Applicants thus respectfully request that the Examiner reconsider and withdraw the outstanding rejection under 35 U.S.C. § 112, first paragraph.

B. Enablement

The Examiner has rejected claims 1-4, 6, 8-34, 38-70, and 74 of the captioned application under 35 U.S.C. § 112, first paragraph, on the basis that "[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims." (Paper No. 11, page 4.) In particular, the Examiner asserts that,

> the specification, while being enabling for use in BHK-21 cells *in vitro* of nucleic acid molecules encoding a heterologous open reading frame and a Sindbis virus non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase with P726S nsP2 and G153E nsP4 mutations, wherein the heterologous open reading frame is operatively linked to a promoter recognized by Sindbis virus RNA-dependent RNA polymerase, does not reasonably provide enablement for the use of these nucleic acids in any other cell type *in vivo or in vitro,* or for the use of any other nucleic acid which lacks a promoter recognized by Sindbis virus RNA-dependent RNA polymerase, or which encodes any other non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase, in any cell. . . .

(Paper No. 11, page 4.) Thus, it is Applicants' understanding that the Examiner asserts that the enablement requirement has not been satisfied for claims 1-4, 6, 8-34, 38-70, and 74 of the captioned application for the following reasons:

1. The disclosure does not enable one skilled in the art to use the claimed nucleic acids, either *in vitro* or *in vivo*, in cells other than BHK-21 cells.

2. The disclosure does not enable one skilled in the art to use nucleic acids which do not have a promoter that is recognized by Sindbis virus RNA-dependent RNA polymerase.

3. The disclosure does not enable one skilled in the art to use nucleic acids which encode a non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase

other than a Sindbis virus RNA-dependent RNA polymerase having the specified mutations at amino acid 726 of nsP2 and amino acid 153 of nsP4.

As discussed below, Applicants respectfully disagree with each of the Examiner's points.

1. The Enablement Requirement

In order to be enabling, the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without "undue experimentation." *Genentech, Inc. v. Novo Nordisk,* 42 U.S.P.Q.2d 1001, 1004 (Fed. Cir. 1997) (citations omitted).

Further, an applicant may rely on the knowledge of those skilled in the art and need not supply information which is well known in the art. *Genentech*, 42 U.S.P.Q.2d at 1005. However, as pointed out by the Examiner, this does not free applicants from disclosing specific starting materials or conditions under which a process can be carried out. *Genentech*, 42 U.S.P.Q.2d at 1005.

Eight factors are to be considered in determining whether undue experimentation is required to practice a claimed invention. *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). These factors include: (1) the quantity of experimentation necessary to practice the invention, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Wands*, 8 U.S.P.Q.2d at 1404 (1988). A conclusion regarding whether the enablement requirement has been satisfied is not a simple factual determination, but must be made by weighing each of the above factors. *See Wands*, 8 U.S.P.Q.2d at 1404.

Further, as noted in *Wands*, a considerable amount of experimentation is permissible if it is merely routine. *Wands*, 8 U.S.P.Q.2d at 1404. As discussed below, Applicants respectfully assert that the present disclosure enables one skilled in the art to practice the claimed invention without undue experimentation.

2. Application of Enablement Factors

Applicants initially note that (1) all eleven of the examples presented in the captioned application are working examples, (2) the art of molecular biology was relatively well developed in March of 1998,[3] (3) the skill level of those in the art in March of 1998 was high (*e.g.*, the skilled artisan would generally have a Ph.D. and experience in techniques related to both viral genetics and tissue culture), (4) the invention is directed to compositions (*e.g.*, DNA molecules) comprising novel and non-obvious combinations of art known or identifiable components, as well as methods for making and using these compositions, and (5) the literal scope of the claims are of a breadth which could be practiced by one skilled in the art in March of 1998 employing teachings of the captioned application and routine amounts of experimentation.

For the sake of simplicity, Applicants address the remaining *Wands* factors, and additional points related to the factors briefly discussed above, as they apply to the Examiner's assertions.

3. Host Cell Range and "In Vivo" Applications

As noted above, the Examiner is apparently of the position that the disclosure does not enable one skilled in the art to use the claimed nucleic acids, either *in vitro* or *in vivo*, in cells other than BHK-21 cells. (*See* Paper No. 11, page 4.) Applicants respectfully disagree.

Applicants begin by noting that claims 25-34 and 61-70 have been canceled and new claims specifically directed to this subject matter are not submitted herewith. Thus, while Applicants reserve the right to pursue the subject matter of claims 25-34 and 61-70 in continuing applications, the Examiner's bases for rejecting claims 25-34 and 61-70 are moot and are not directly addressed herein.

Applicants assert that, with respect to host cell range, the enablement requirement is satisfied for new claims 75-125 if one skilled in the art is able to identify cells without undue experimentation

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[3]Applicants do not believe that it is necessary to provide evidence to support this statement, but will do so at the request of the Examiner.

that are suitable for practicing the claimed invention. Applicants note along these lines that the inventors and co-workers have confirmed that the pCYTts vector replicates in the following cells lines: BHK-21, CHO-k1, COS-7, 293, 293T, C2C12, BF, MC57, HepG2, and Vero.[4]

Further, one skilled in the art would know that it might be necessary to screen several cell lines before finding one which will support replication of a particular nucleic acid of the invention. *See, e.g., In re Wands*, 8 U.S.P.Q.2d at 1406-1407 (It is not undue experimentation for practitioners of the monoclonal antibody art to be prepared "to screen negative hybridomas in order to find one that makes the desired antibody."). Such experimentation would be routine and, thus, could be accomplished without undue experimentation using teachings of the captioned application. Applicants note along these lines that the specification clearly indicates that at least one nucleic acid of the invention (*i.e.*, pCYTts) replicates in BHK-21 cells. Thus, one skilled in the art is guided by the captioned application to use nucleic acids of the invention in BHK cell lines.

In addition, if BHK cell lines are not suited for the skilled artisan's particular purpose (*e.g.*, do not result in the production of a protein having a desired glycosylation pattern), then this individual would know to use another cell line. One skilled in the art would thus routinely test cell lines to identify those which are suitable for the specific application (*e.g.*, support replication of the particular nucleic acid used and generate a protein having a desired glycosylation pattern).[5] In other words, the skilled artisan would follow either the same or a similar path as that set out in Agapov *et al., Proc. Nat. Acad. Sci. USA 95*:12989-12994 (1998) (Agapov *et al.*), [Document U], which the Examiner

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[4]Applicants will submit a declaration under 37 C.F.R. § 1.132 to support this statement if the Examiner so requests.

The inventors and co-workers have found that the pCYTts vector does not replicate in HeLa cells and are bringing this forth in the interest of full disclosure. Applicants note, however, that claims may encompass inoperative embodiments unless "the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention . . . ." *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 224 U.S.P.Q. 409, 414 (Fed. Cir. 1984) (citation omitted).

[5]Again, Applicants will submit a declaration under 37 C.F.R. § 1.132 to support these statements if the Examiner so requests.

cites as setting forth the state of the art (Paper No. 11, page 7), in identifying suitable cells with which to practice particular embodiments of the invention.

As suggested above, the Examiner asserts that Agapov *et al.* sets forth the state of the art regarding "the use of DNA molecules encoding non-cytopathic RNA-dependent RNA polymerases and heterologous open reading frames." (Paper No. 11, page 7.) The Examiner then states that Agapov *et al.* describes experiments in which:

> Sindbis virus-based vectors comprising a mutation at position 726 of nsP2 were used to express heterologous proteins in cultured cells. While RNA replication was obtained in BHK-21 and CHO cells, and to a lesser extent in Vero cells, replication was not observed in any other cell type tested, including primary chicken fibroblasts, MDBK, MDCK, 293, HeLa, and PC12 cells. *All of these cells support RNA replication by cytopathic polymerases, and the reason why replication by non-cytopathic polymerases is not supported is unknown. . . .*

(Paper No. 11, page 7 (emphasis added).) As already indicated, in contrast to the results obtained with the vector of Agapov *et al.*, Applicants have found that the pCYTts vector replicates in 293 cells. In addition, Applicants note that the vectors used in Agapov *et al.* are not identical to the pCYTts vector. Thus, the host cell range data presented in Agapov *et al.* will not necessarily correlate with the host cell range of the pCYTts vector or other nucleic acids of the invention.

Further, assuming, *arguendo*, that the vectors disclosed in Agapov *et al.* have the same host cell range as nucleic acids of the invention, Agapov *et al.* demonstrates that three different cell types support replication. Thus, assuming that the data present in Agapov *et al.* actually does correlate with the host cell range of nucleic acids of the invention, this paper does not support the position that the claims should be limited to use in a single type of host cell (*i.e.*, BHK-21 cells).

Applicants point out that the Examiner's statement relating to it not being known why particular Sindbis virus-based vectors (*i.e.*, vectors which encode a non-cytopathic RNA-dependent RNA polymerase) appear to replicate in some cells but not others is not directly relevant to whether the enablement requirement has been satisfied for canceled claims 1-4, 6, 8-24, 38-60, and 74 or new claims 75-125. More specifically, Applicants note that, in addition to Applicants' data not being

entirely consistent with the data present in Agapov *et al.*, it is not necessary for applicants to understand how their invention works. *In re Cortright*, 49 U.S.P.Q.2d 1464, 1469 (Fed. Cir. 1999) (citations omitted).

The Examiner also asserts that:

> Claims 32-34 and 68-70 are specifically directed to pharmaceutical compositions comprising a nucleic acid as the active ingredient. For the purpose of examination under 35 U.S.C. 112, first paragraph, pharmaceutical compositions must be enabled for therapeutic use. Thus claims 32-34 and 68-70 are drawn specifically to gene therapy, particularly in light of the specification at page 1, lines 17-19, and pages 33-37. Claims 25-31 and 61-67 are drawn to the use of the nucleic acids of the invention in humans, and have no asserted utility other than gene therapy. *Because the specification asserts a use for the claimed nucleic acid molecules in gene therapy, all of the claims, when read in light of the specification, read on gene therapy.* The asserted utilities of the invention also encompass the construction of transgenic animals comprising the claimed nucleic acids, and the expression of RNAs and polypeptides in cultured cells.[6]

(Paper No. 11, page 5 (emphasis added).)

As noted above, Applicants have canceled all of the claims referred to above (*i.e.*, claims 25-34 and 61-70) and do not submit new claims herein directed to the subject matter of these canceled claims. However, Applicants respectfully disagree with the italicized statement and are confused by the last sentence of the block quote set out above. Applicants believe, however, that the Examiner has inappropriately read limitations into the claims based on the specification.

Applicants note that when a claim does not recite a specific utility, applicants need only show a single utility to satisfy 35 U.S.C. § 112. *See Raytheon Co. v. Roper Corp.*, 220 U.S.P.Q. 592, 598-599 (Fed. Cir. 1983). Several examples are provided in the captioned application which show

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[6]Applicants note that the Office Action mailed April 4, 2000 (Paper No. 9) states that original claims 35-37 and 71-73, directed to transgenic animals, represent a different invention than that defined by original claims 1-34, 38-70 and 74. (Paper No. 9, page 2.) Further, the invention defined by claims 1-34, 38-70 and 74 was provisionally elected by Applicants in the Reply to Restriction Requirement and Election of Species filed May 24, 2000 and made final by the Examiner in the current Office Action. (Paper No. 11, page 2.) Thus, claims specifically directed to transgenic animals are not currently before the Examiner.

that nucleic acids of the invention can be used to both regulate the expression of encoded proteins in cells grown in culture and produce RNA replicons. (*See, e.g.,* Specification page 43, line 9, to page 52, line 25.) Applicants assert that no more is needed.

In other words, Applicants need not show that nucleic acids and methods which fall within the scope of canceled claims 1-4, 6, 8-24, 38-60, and 74 or new claims 75-125 are suitable for gene therapy applications or the construction of transgenic animals. It is enough that nucleic acids and methods of the invention can be used, for example, for the production of expression products in cells grown in culture.

With the above in mind, Applicants assert that nucleic acids of the invention will replicate in a number of eukaryotic cell lines. Further, if one skilled in the art attempted to practice the invention using a cell line in which the particular nucleic acids would not replicate, then the skilled artisan would merely try a different cell line. For example, the skilled artisan might attempt to practice the invention using BHK-21 cells, as described in the captioned application. However, if BHK cell lines are not suitable for the particular application, then the skilled artisan would know to use a suitable one.

Applicants thus assert that nucleic acids and methods of the invention can be used with cell cultures without undue experimentation and no more is needed to satisfy the enablement requirement.

4. RNA-Dependent RNA Polymerase Promoters

The Examiner also appears to be of the position that the captioned application does not enable one skilled in the art to use nucleic acids of the invention which do not have a promoter that is recognized by Sindbis virus RNA-dependent RNA polymerase. (*See* Paper No. 11, page 4.) In particular, the Examiner asserts that, "[d]isclosure of a single polynucleotide encoding one non-cytopathic, temperature-sensitive RNA dependent RNA polymerase, and one promoter recognized by that polymerase, is enabling only for that particular polynucleotide and degenerate ones encoding the same polymerase." (Paper No. 11, page 6.) The Examiner further states that "the captioned application . . . does not reasonably provide enablement . . . for the use of any other nucleic acid

which lacks a promoter recognized by Sindbis virus RNA-dependent RNA polymerase." (Paper No. 11, page 4.) Again, Applicants respectfully disagree.

Applicants note that the captioned application clearly states that subgenomic promoters, a promoter type which binds RNA-dependent RNA polymerase, suitable for use with the invention can be obtained from viruses. (Specification, page 21, lines 19-22.) Further, the captioned application provides a number of examples of viruses, including Sindbis virus, Semliki Forest Virus (SFV), and Venezuelan equine encephalomyelitis virus (VEE), which contain promoters that bind RNA-dependent RNA polymerases. (*See, e.g.*, Specification, page 14, lines 21-30.)

Additionally, a number of promoters which can be used in nucleic acids of the invention were known in the art in March of 1998. For example, Figure 19 of Strauss *et al., Microbiol. Rev. 58*:491-562 (1994) (Strauss *et al.*) [Document AS24], provides an alignment of subgenomic promoter sequences from twelve different viruses.[7] More recently, Zhang *et al., Gene Ther. 4*:367-374 (1997) [Document AS41], describe the construction of vectors which contain an SFV subgenomic promoter. Further, Pushko *et al., Virology 239*:389-401 (1997) [Document AT37], describe VEE replicons which contain a subgenomic promoter. In addition, Wang *et al., Virol. 232*:174-186 (1997) [Document AT40] describe two subgenomic promoters of the turnip crinkle virus. Thus, one skilled in the art in early 1998 clearly had the tools readily available, using the guidance provided in the captioned application, to make and use nucleic acids of the invention which contain promoter elements derived from a variety of different viruses that bind RNA-dependent RNA polymerases.

5. RNA-Dependent RNA Polymerases

The Examiner also appears to be of the position that the disclosure does not enable one skilled in the art to use nucleic acids of the invention which encode non-cytopathic, temperature-sensitive RNA-dependent RNA polymerases other than Sindbis virus RNA-dependent RNA polymerase. (*See* Paper No. 11, page 4.) Once again, Applicants respectfully disagree and note that

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[7]Applicants note that Strauss *et al.* [Document AS24] has been incorporated by reference into the captioned application. (Specification, page 14, line 23; page 57, lines 8-10.) Applicants do not believe that it is necessary to directly incorporate text from Strauss *et al.* into the specification or sequence listing to provide support for the claims, but will do so at the request of the Examiner.

one skilled in the art in March of 1998 seeking to use a non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase would have been able to obtain such an enzyme from at least two different sources. More specifically, the skilled artisan could either prepare nucleic acid encoding a non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase from components available in the art or could generate nucleic acid encoding such polymerases.

a. Non-Cytopathic, Temperature-Sensitive RNA-Dependent RNA Polymerase Components Known in the Art

A number of mutations in nsP2 and nsP4, in addition to those described in the captioned application, were known in the art in March of 1998 to render RNA-dependent RNA polymerases either non-cytopathic or temperature sensitive. For example, Frolov *et al.*, *Proc. Natl. Acad. Sci. USA 93:*11371-11377 (1996) (Frolov *et al.*) [Document AS7], describe two Sindbis based replicons which exhibit a non-cytopathic phenotype. The mutation in each of these replicons maps to the nsP2 gene. In addition, Khromykh *et al.*, *J. Virol. 71*:1497-1505 (1997) (Khromykh *et al.*) [Document AS33], describe Flavivirus Kunjin subgenomic replicons which express a non-cytopathic RNA-dependent RNA polymerase. (*See* Khromykh *et al.*, page 1504, top of second column.)

Further, a number of temperature-sensitive RNA-dependent RNA polymerases were known in the art well before March of 1998. For example, Burge *et al.*, *Virology 30*:214-223 (1966) (Burge *et al.*) [Document AS4], describe eleven temperature sensitive Sindbis viruses having mutations which map to five different complementation groups. Also, Suopanki *et al.*, *J. Gen. Virol. 79*:309-319 (1998) (Suopanki *et al.*) [Document AT29], describe a temperature-sensitive SFV RNA-dependent RNA polymerase having an alteration in amino acid 781 of nsP2. (*See* Suopanki *et al.*, text abridging pages 311-312.) Suopanki *et al.* also describe a number of temperature sensitive Sindbis mutants, designated ts15, ts17, ts24, and ts133. (Suopanki *et al.*, page 312, first column, first full paragraph.)

Further, Strauss *et al.* [Document AS24] note at the bottom of the first column through the top of the second column on page 511 that, at the time this review article was written, a series of

temperature-sensitive mutants of nsP4, having differing activities at the restrictive temperature, were known in the art.

b. Preparation of Temperature Sensitive, Non-Cytopathic RNA-Dependent RNA Polymerases

In addition to being able to construct nucleic acids which encode temperature-sensitive, non-cytopathic RNA-dependent RNA polymerases from art known components, one skilled in the art could also use art known techniques to prepare RNA-dependent RNA polymerases suitable for use with the invention.

As noted in the captioned application, methods for generating mutants are known in the art. (*See, e.g.,* Specification, page 21, lines 29-30; page 22, lines 3-25.) In addition, Frolov *et al.* [Document AS7], for example, describe a method for identifying non-cytopathic RNA-dependent RNA polymerases.[8] According to this method, replicons which express the dominant, selective marker, puromycin acetyltransferase but lack nucleotide sequences which encode structural protein are transfected in BHK cells. Puromycin resistant clones are then selected.

With respect to the construction and selection of temperature-sensitive RNA-dependent RNA polymerases, Applicants note that methods for identifying such RNA-dependent RNA polymerases have been known in the art for some time. (*See, e.g.*, Burge *et al., Virology 30*:214-223 (1966) (Burge *et al.*) [Document AS4].) The captioned application notes that temperature sensitivity may be conferred, for example, by the introduction of a mutation in the nsP4 gene. (Specification, page 22, lines 13-17.) The captioned application then refers to a particular mutation in a specific nsP4 gene (*i.e.*, the Sindbis nsP4 gene) which renders the RNA-dependent RNA polymerase temperature-sensitive and to two publications which describe methods for identifying temperature-sensitive mutants. (Specification, page 22, lines 17-22.)

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[8]Frolov *et al.* has been incorporated by reference into the captioned application. (Specification, page 50, lines 9-10; and page 57, lines 8-10.) Again, Applicants do not believe that it is necessary to import text from Frolov *et al.* into the captioned application to provide support for the claims, but will do so at the request of the Examiner.

In view of the above, Applicants assert that one skilled in the art could prepare temperature-sensitive, non-cytopathic RNA-dependent RNA polymerases suitable for use with the invention using both information known in the art and disclosed in the captioned application.

c. Art Known Vectors and cDNAs

Viruses suitable for preparing nucleic acids of the invention will normally both encode RNA-dependent RNA polymerases and have functional RNA-dependent RNA polymerase binding elements.[9] Further, a number of non-Sindbis virus based vectors and cDNAs which employed RNA-dependent RNA polymerases were known in the art in March of 1998. (*See, e.g.*, Davis *et al., J. Virol. 70*:3781-3787 (1996) [Document AR32]; Caley *et al., J. Virol. 71*:3031-3038 (1997) [Document AS31]; Pushko *et al., Virology 239*:389-401 (1997) [Document AT37]; Roks *et al., Cardiovasc. Res. 35*:498-504 (1997) [Document AS38]; Zhang *et al., Gene. Ther. 4*:367-374 (1997) [Document AS41]; Kohno *et al., Gene. Ther. 5*:415-418 (1998) [Document AS34]; and Turina *et al., Virol. 241*:141-155 (1998) [Document AR40].)

As evidenced by the above and the amount of material Applicants have submitted in prior Information Disclosure Statement (IDSs) and the accompanying IDS, a considerable amount of information was known in March of 1998 about viral systems which can be adapted for use in the invention.

In view of the above, Applicants assert that one skilled in the art could practice the full scope of the new claims 75-125. Applicants thus respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement.

VII. The Rejections under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 4, 16-19, 21, 22, 41, and 52-58 "under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." (Paper No. 11, page 9.)

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[9]Applicants do not mean to imply that the invention does not encompass synthetic nucleic acids which perform essentially the same functions as those derived from viruses.

A. Claims 4 and 41

The Examiner asserts that, "[c]laims 4 and 41 are indefinite because the specification fails to unambiguously define the term 'undetectable'. . . ." (Paper No. 11, page 9.) The Examiner notes that the term "undetectable" is defined in the specification but then states that "the definition of 'undetectable' varies with the assay [used]." (Paper No. 11, page 9.) Applicants respectfully disagree but have canceled claims 4 and 41 and submit new claims 82 and 105 to address the Examiner's concerns. More specifically, new claims 82 and 105 recite that the encoded RNA-dependent RNA polymerase has replicase activity at 34°C which is at least five fold lower than the replicase activity at 29°C. Applicants note that new claims 82 and 105 are supported by the specification, *inter alia*, at page 15, lines 22-26.

B. Claims 16-22 and 52-58

The Examiner asserts that claims 16-22 and 52-58 "are incomplete because they lack a critical method step." (Paper No. 11, page 10.) In particular, the Examiner asserts that claims 16-19, 21-22, 52-55 and 57-58 "recite no step at which the polypeptide or RNA is expressed." (Paper No. 11, page 10.) The Examiner also asserts that claims 20 and 58 "recite no step at which alphaviral particles are produced." (Paper No. 11, page 10.)

To address the Examiner's concerns, facilitate prosecution, and to clarify the subject matter which Applicants believe is the invention, Applicants have canceled claims 16-17, 20-21, 52-53 and 56 and submit new claims herein (*i.e.*, claims 93-94, 97-98, 116-117, and 120) which contain, where appropriate, either "expression" or "production" steps.

C. Conclusion

In view of the cancellation of claims 4, 16-19, 21, 22, 41, and 52-58 and the format of the new claims submitted herein, Applicants respectfully request that the Examiner reconsider and withdraw the above rejections under 35 U.S.C. § 112, second paragraph.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all currently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

It is not believed that extensions of time are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor are hereby authorized to be charged to our Deposit Account No. 19-0036.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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